

## REMARKS

### I. Introduction

Applicants acknowledge receipt of the Final Office Action mailed August 9, 2004 and the Advisory Office Action mailed December 20, 2004. Claim 96 has been added. Claims 36, 38, 42-49, 51, and 96 remain pending in the application. Claims 36, 38 and 51 have been amended. No new matter has been added by these amendments. This Amendment supercedes the amendment filed on December 2, 2004.

### II. Claim Rejections

#### A. Claim Rejections Under 35 U.S.C. § 102

The Examiner has declined to enter the after-final amendment that Applicants filed in the U.S. Patent and Trademark Office on December 2, 2004 because it allegedly introduces new limitations, including the consumption of all phosphate in the fermentation medium prior to a second addition of phosphate and maintenance of the phosphate concentration. The Examiner has also alleged that the potassium phosphate salts recited in claim 45 are anticipated by the potassium phosphate salts used in *Cole et al.*

Applicants respectfully traverse this rejection and request reconsideration of Applicants' response filed December 2, 2004. In order to reject a claim under 35 USC § 102, the Examiner must demonstrate that each and every claim element is contained in a single prior art reference. *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 90 (Fed. Cir. 1986); *see also* MPEP § 2131 (August 2001). That one skilled in the art might interpret a prior art reference as teaching a feature of the claimed invention required for anticipation is not sufficient. *Finnigan Corp. v. Int. Trade Com'n.*, 180 F.3d 1354, 51 USPQ2d 1001 (CAFC 1999).

Applicants respectfully submit that the claims, as amended, are distinct from Cole *et al.* and do not introduce any new limitations. As mentioned in Applicants' previous response, the maintenance of the phosphate source after the initial phosphate source is consumed in the present invention is supported in the specification at page 11, last paragraph - "The pH value reached *in the first hours of the culture growth* rose to almost 7.5. *During this time phosphorus was consumed*, and clavulanic acid started to be produced ..." (emphasis added). Thus, the assimilable source of phosphorus is consumed after the first hours of fermentation. Following the consumption of this initial phosphorus source, the concentration of assimilable phosphorus sources in the fermentation broth were used during the growth phase of the fermentation (page 10, last line to page 11). Nevertheless, and without acquiescing in the rejection, Applicants have made amendments to claim 36 for further clarity.

Applicants respectfully submit that Cole *et al.* do not teach that sodium or potassium salts must be added to the medium after the starting medium is consumed, as in the present invention. Rather, Cole *et al.* teach that "Na<sup>+</sup> or K<sup>-</sup> salts of phosphoric acid *may* be added to the media ..." (emphasis added) (col. 10, lines 55-57). Cole *et al.* neither teaches or suggests that the phosphorus concentration is maintained below 0.15% w/v during the growth phase of the fermentation after the phosphorus present in the starting medium is consumed or that the phosphorus in the starting medium is allowed to decrease after cessation of the growth phase. Even if several of the examples of Cole *et al.* teach the use of phosphorus in the starting cultivation medium, and even if the allegedly inherent characteristic of phosphorus decreasing in the medium after the growth phase of the fermentation necessarily flows from the teaching of Cole *et al.*, as the examiner apparently contends, this alleged feature of Cole *et al.* is irrelevant in

light of the claimed invention because the phosphorus concentration is maintained during the growth phase of fermentation after the initial phosphorus present in the media is consumed. Therefore, Applicants respectfully request that the Examiner withdraw these rejections.

**B. Claim Rejections Under 35 U.S.C. § 103(a)**

The Examiner has maintained the rejection of claims 45 and 46 under 35 U.S.C. § 103(a) as being obvious over Cole *et al.*'s disclosed use of potassium dihydrogen phosphate as the phosphorus source. The Examiner also has alleged that one of ordinary skill in the art would reasonably expect the salts of potassium and sodium to function substantially equivalently in the processes disclosed by Cole *et al.* in view of Cole *et al.*'s disclosure that either of the salts of phosphoric acid may be used because both sodium and potassium phosphate salts are well known in the fermentation arts and are equivalent to the extent that they are both suitable in the preparation of aqueous solutions. The Examiner has further alleged that while the increase in clavulanic acid production using sodium salt instead of potassium salt is not specific to a particular microbial strain, the significantly increased yield obtained from using sodium salt instead of potassium salt taught by Cole *et al.* comes from a specific set of fermentation conditions which produce specific clavulinic acid yields.

Applicants respectfully traverse these rejections. M.P.E.P. § 2142 sets forth three requirements that must be met in order to establish a *prima facie* case of obviousness under § 103. First, there must be some suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the references. Second, there must be a reasonable expectation of success upon combining such references. Finally, the prior art references, when combined, must teach or suggest all of the claim limitations.

Applicants respectfully submit that the unexpected result of a significantly improved clavulanic acid yield in the present invention is not due to some unclaimed aspect of the present invention. Rather, the clavulanic acid yield is the direct result of the consumption of the starting phosphorus source after a fermentation time of 40 hours (*see* specification, page 3, paragraphs 1-2), followed by the maintenance of the phosphorus source (phosphate) concentration in the range of between 0.0015% w/v and 0.15% w/v during the growth phase, as recited in claim 36. This unexpected result is achieved regardless of any specific fermentation conditions not recited in claim 36, and does not depend on the type of clavulinic acid-producing *Streptomyces* species or phosphate source used.

Because the unexpected result does not depend on what *Streptomyces* species is used, the fermentation conditions, including the specific concentrations of the fermentation additives, do not need to be defined more specifically in claim 36 because the concentrations of the fermentation components depend upon the characteristics of the *Streptomyces* species used in the fermentation (*see* page 3, paragraph 3 of the specification). Applicants note that Example 1B on pages 9-10 of the specification describes a yield of 3,580 mg/l (3,580 µg/ml) of clavulanic acid obtained from *Streptomyces sp 6621 FERM P2804* (*see* page 3, paragraph 2 of the specification), which is significantly and unexpectedly higher than the prior art processes cited by the Examiner (i.e., 200-500 µg/ml cited in Examples 12 and 13). This shows that the unexpected results of the present invention do not merely arise from the substitution of one *Streptomyces clavuligerus* strain for another.

Applicants also point to the declaration filed with Applicants' previous response on December 2, 2004, which includes an additional fermentation example of clavulanic acid using the microorganism *Streptomyces clavuligerus ATTC 27064* (*see* Declaration, tab D of the

Appendix) which also gives an unexpectedly high yield of clavulanic acid (4410 µg/ml) (*see* page 1, paragraph 3 and page 4, lines 10-11 of the specification, arguing that the invention gives improved yields of clavulanic acid from *S. clavuligerus*). Finally, in Example 1(a), *Streptomyces sp. PP 6621 FERM P2804* is used. Applicants further note that the additional strain *S. clavuligerus ATTC 27064*, disclosed in the declaration, is identical to the strain *S. clavuligerus NRRL 3585* disclosed in the specification (*see* specification at page 1, paragraph 3 and page 4, second paragraph; Declaration, tab E of the Appendix). Thus, Applicants submit that it is not necessary to claim a specific set of fermentation conditions disclosed in the specification, such as sodium salt, instead of the potassium salt taught by Cole *et al.*, or a specific clavulinic acid yield. The phosphorus source initially present in the medium is allowed to be consumed before the phosphorus concentration is maintained between 0.0015% and 0.15% during the growth phase of fermentation (page 3, lines 2-5 of the specification), which regulates the synthesis of clavulanic acid and/or its salts and contributes to the increased clavulinic acid yield (page 3, second paragraph of the specification).

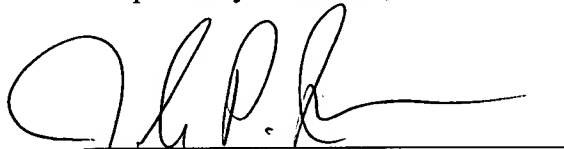
Applicants respectfully submit that the starting concentration of phosphorus and the maintenance of the phosphorus source concentration in claim 36 are not disclosed or suggested by Cole *et al.*, either alone, in combination with, or in view of Stanbury *et al.* or Puentes *et al.* While Cole *et al.* disclose various concentrations of assimilable phosphorus yielding various amounts of clavulanic acid, and Cole *et al.* teach that phosphate should be included in the fermentation medium, Cole *et al.* do not teach that the maintenance of the phosphorus source concentration is essential during the growth phase of fermentation. Nor do Cole *et al.* show any relationship between the phosphate present in the starting medium, the maintenance of the phosphate source concentration, or the yield of clavulanic acid achieved.

The results of the present invention are unexpected and unobvious in view of Cole *et al.* because Cole *et al.* do not teach consumption of the phosphorus source (phosphate) present at the beginning of the fermentation, followed by the maintenance of the phosphorus source (phosphate) below a limit of 0.15% w/v during the growth phase of fermentation, *after* which the phosphorus concentration is allowed to decrease. Neither do Cole *et al.* show any relationship between the phosphate present in the starting fermentation medium or the maintenance of the phosphate concentration during the growth phase of fermentation. Thus, Applicants submit that the claimed invention is unobvious in view of Cole *et al.*, either alone, or in combination with Stanbury *et al.*, and Puentes *et al.*

#### IV. Conclusion

In view of the foregoing remarks and amendments, reconsideration of this application and allowance of the claims are respectfully requested. If any issues remain which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at 202-912-2777.

Respectfully submitted,



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